downstream of the promoter and upstream of the heterologous gene; and (d) a polyadenylation sequence positioned downstream of the heterologous gene.

REMARKS

The Present Invention

The present invention is directed to an adenoviral vector for expressing a heterologous gene(s) in a host cell, a host cell infected with such a vector, a method of producing a selected protein by culturing a host cell infected with such a vector, and a method of delivering a heterologous gene to an animal heart *in vivo* by administering such a vector to the animal heart.

Discussion of the Amendment to the Specification

The specification has been amended to correct an obvious typographical error. The example set forth on page 35 has been amended to recite "Example X," instead of "Example VIII." In that the specification was amended only to correct a typographical error, no new matter has been added by way of this amendment.

Discussion of Amendments to the Claims

Claims 1, 3, 4, 9 and 17 have been amended and claims 2, 7, 8, 10, 11 and 13-15 have been cancelled to point out more particularly and claim more distinctly the present invention. Claim 1 has been amended to recite an adenoviral vector. The amendment to claim 1 is supported by the specification at, for example, page 9, lines 22-32, page 16, line 26, through page 17, line 7, page 18, line 11, through page 19, line 13, and Examples 9 and 10. Claims 3, 4, 9 and 17 have been amended to recite an adenoviral vector in view of the amendment to claim 1. Claims 1 and 3 have additionally been amended to correct matters of form. Claim 4 has been amended to recite the mouse β-globin polyadenylation sequence. Support for claim 4 is found in the specification at, for example, page 9, lines 11-21. Claims 18-20 are new. Claims 18 and 19 correspond to canceled claims 13 and 15, respectively, except that claims 18 and 19 recite an adenoviral vector, support for which is as indicated above, and claim 19 has been further amended to address matters of form. The addition of claim 20 is supported by the specification at, for example, page 10, lines 14-27, page 16,

line 26, through page 17, line 7, and Example 10. No new matter has been added by way of these amendments.

The Pending Claims

Claims 1, 3, 4, 9 and 17-20 are currently pending. Claims 1, 3, 4, 9 and 17 are directed to the adenoviral vector, whereas claim 18 is directed to the host cell, claim 19 is directed to the method of producing a selected protein and claim 20 is directed to a method of administering a heterologous gene to an animal heart *in vivo*. The text of the pending claims as amended is set forth on an attachment hereto for the convenience of the Examiner.

Summary of Previous Office Action

In the Office Action of August 23, 1999, the Office rejected claims 14 and 15 under 35 U.S.C. § 112, first paragraph, and claims 1, 3, 4, 7 and 14 under 35 U.S.C. § 112, second paragraph. Claims 1-4, 7-11, 13-15 and 17 were rejected under 35 U.S.C. § 103(a). Reconsideration of these rejections is hereby requested.

Discussion of Rejection under Section 112, First Paragraph

The Office has rejected claims 14 and 15 as allegedly not enabled for host cells *in vivo*. The Office alleges that, while techniques for obtaining stable gene expression in cultured cells are discussed, no corresponding techniques for whole animals are mentioned. The Office additionally contends that techniques for delivering the recombinant adenovirus to appropriate mammalian tissues are not discussed. According to the Office, given the unpredictable nature of the *in vivo* environment, in the absence of such guidance, the artisan would have been required to exercise undue experimentation to practice the invention *in vivo*. This rejection is traversed for the reasons set forth below.

Contrary to the contention of the Office, the instant application provides sufficient guidance as to allow one of ordinary skill in the art to make and use the present invention *in vivo*, as well as *in vitro*. For instance, Example 10 (page 35, line 7, through page 44, line 4) describes a method of constructing an adenoviral vector in accordance with the present invention and delivering the adenoviral vector to heart cells *in vitro* and *in vivo*. Methods of determining protein expression are also set forth in Example 10. In addition to the disclosure of the instant specification, at the time of

filing of the parent application, methods for delivering adenoviral vectors to various tissues *in vivo*, such as lung and muscle, to obtain protein expression were set forth in the literature (see, for example, page 5, lines 14-25). Therefore, in view of the disclosure of the instant specification and the state of the art at the time of filing of the parent application, one of ordinary skill in the art would have had sufficient guidance to make and use the present invention *in vitro* and *in vivo* using routine experimentation. The present invention is completely enabled and, therefore, the rejection of claim 15, now claim 19 (claim 14 has been cancelled), should be withdrawn.

Discussion of Rejection under Section 112, Second Paragraph

The Office has rejected claims 1, 3, 4, 7 and 14 as allegedly indefinite for failing to point out particularly and claim distinctly the present invention. Applicant submits that the rejection is moot in view of the amendments to claims 1, 3 and 4 and the cancellation of claims 7 and 14.

Discussion of Rejection under Section 103(a)

The Office has rejected claims 1-4, 13-15 and 17 as allegedly being obvious in view of and, therefore, unpatentable over Kirshenbaum et al., *J. Clin. Invest.*, *92*, 381-389 (1993); Quantin et al., *Proc. Natl. Acad. Sci. USA*, *89*, 2581-2584 (1992); or Stratford-Perricaudet et al., *J. Clin. Invest.*, *90*, 626-630 (1992); in view of Huang et al., *Nucl. Acid Res.*, *18*(4), 937-347 (1990); Choi et al., *Mol. Cell. Biol.*, *11*(6), 3070-3074 (1991); Keating et al., *Exp. Hematol.*, *18*, 99-102 (1990); and WO 91/00747 (KabiGen et al). This rejection is traversed for the reasons set forth below.

Claims 1, 3, 4 and 17 have been amended to recite an adenoviral vector. Claims 2 and 13-15 have been cancelled; claims 18 and 19 correspond to claims 13 and 15. Thus, the pending claims, as amended, are directed to an adenoviral vector for expressing a heterologous gene(s) in a host cell, a host cell transformed with such a vector, and a method of using such a vector to produce a selected protein. The adenoviral vector comprises (a) at least one insertion site for cloning a selected heterologous gene; (b) a promoter sequence positioned upstream from the at least one insertion site, wherein, upon cloning of the heterologous gene into the at least one insertion site, the gene is under the regulatory control of the promoter; (c) a eukaryotic splice acceptor and donor site positioned downstream of the promoter and

upstream of the insertion site; and (d) a polyadenylation sequence positioned downstream of the insertion site.

Quantin et al., Kirshenbaum et al., and Stratford-Perricaudet et al. do not teach or suggest the use of a splice acceptor and donor site located between a promoter sequence and a heterologous gene to be expressed, the mouse CMV early promoter, and the mouse β-globin polyadenylation sequence. While the Office cites Huang et al., Choi et al., Keating et al., and KabiGen et al. as curing the deficiencies of Quantin et al., Kirshenbaum et al., and Stratford-Perricaudet et al., such is not the case. While Huang et al. may disclose the use of a splice acceptor site, such a disclosure is in the context of plasmid vectors – not adenoviral vectors. While Choi et al. may disclose the use of an intron between a promoter and a gene to be expressed, such a disclosure is in the context of chromosomes – not adenoviral vectors. The disclosure of the use of the murine immediate early CMV promoter by Keating et al. and the disclosure of the use of a rodent β-globin polyadenylation sequence and multiple cloning sites in vectors for insertion of an additional gene sequence by KabiGen et al. are also not in the context of adenoviral vectors.

In spite of the fact that the secondary references are not directed to adenoviral vectors, the Office contends that one of ordinary skill in the art would have been motivated to combine the disclosures of the primary and secondary references because of the disclosed value of the disclosed components to increase gene expression in other contexts and because each component would have been expected to function in the same manner in an adenoviral vector. Yet, the ordinarily skilled artisan would not have expected a splice site to function in such a manner in adenovirus, as evidenced by the Declaration under 37 C.F.R. § 1.132, executed by Dr. Imre Kovesdi and submitted herewith.

As set forth by Dr. Kovesdi, the nature of adenoviral vectors is a great deal more complex than that of plasmids and most other viral vectors. The adenoviral genome is larger, and its organization is more complex than other DNA and viral vectors, such as retrovirus and adeno-associated virus. In addition, within a host cell, the adenoviral genome is non-covalently bound to the nuclear matrix through the adenoviral terminal protein, whereas a plasmid, such as that disclosed in Huang et al., typically exists as an episomal, free-floating DNA template. Due to the complex nature of adenovirus, regulatory sequences may have different activity in adenovirus

than in other expression systems. For example, the SV40 promoter is known in the art to be a relatively strong promoter in nature. In adenovirus, however, SV40 is a relatively weak promoter.

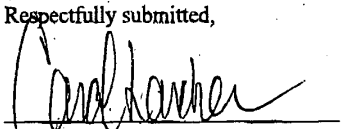
With respect to splicing, unlike other expression systems, adenoviral genomes comprise numerous splice sites and most primary transcription units are extensively spliced. In some instances, a single primary transcript can give rise to more than 30 mRNA species. Moreover, splicing in adenovirus is a highly regulated process and alternative splicing is common. In many adenoviral genes, splicing varies during the course of infection. Therefore, in light of the complexity of adenovirus, the ordinarily skilled artisan would not have expected a splice site, such as those described by Huang et al. and Choi et al., to behave similarly in an adenoviral vector.

In view of the above, Applicant respectfully submits that one of ordinary skill in the art would not have had a reasonable expectation of success that incorporation of a splice site, such as those disclosed by Huang et al. or Choi et al., into an adenoviral vector would have enhanced expression of a heterologous gene cloned into the adenoviral vector. Accordingly, Applicant requests withdrawal of the rejection under Section 103(a).

Conclusion

The application is considered to be in good and proper form for allowance, and the Examiner is respectfully requested to pass this application to issue. If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned attorney.

Respectfully submitted,

By: 

Carol Larcher, Reg. No. 35,243
One of the Attorneys for Applicant
LEYDIG, VOIT & MAYER, LTD.
Two Prudential Plaza, Suite 4900
180 North Stetson
Chicago, Illinois 60601-6780
(312) 616-5600 Telephone
(312) 616-5700 Facsimile

Date: May 30, 2000

In re Appln. of Falck-Pe[illegible]sen
Serial No. 08/653,114

CERTIFICATE OF FACSIMILE TRANSMISSION

I hereby certify that the attached PRELIMINARY AMENDMENT, (7 pgs.) PENDING CLAIMS AFTER AMENDMENT (2 pgs.), DECLARATION UNDER 37 C.F.R. § 1.132 (5 pgs.), 4 references (27 pgs.), transmittal (in duplicate) (2 pgs.), Curriculum Vitae of Dr. Imre Kovesdi (8 pgs.), and Certificate of Facsimile Transmission (1 pg.) is being transmitted via facsimile to Examiner Richard Schnizer, United States Patent and Trademark Office, Washington, D.C. 20231, at Facsimile No. (703) 308-8724, on the date shown below.

Date: May 30, 2000

Frances Sanchez